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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/576,121

01/22/2007

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9516-314-999

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09/16/2008

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EXAMINER

MANOHAR, MANU M

ART UNIT

PAPER NUMBER

4161

MAIL DATE

DELIVERY MODE

09/16/2008

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.



## **DETAILED ACTION**

### **The status of the Claims**

Claims 49, 57-64 are pending in the application.

### **Priority**

This application has the filing date of January 22, 2007 and is a national stage application of PCT/US04/13252, filed April 28, 2004 and claims the benefit of CIP of 10/699,154 of October 30, 2003. This application is considered with the priority date of April 28, 2004.

If applicant desires to claim the benefit of a prior-filed application under 35 U.S.C. CIP of 10/699154, a specific reference to the prior-filed application in compliance with 37 CFR 1.78(a) must be included in the first sentence(s) of the specification following the title or in an application data sheet. For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications.

If the instant application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35

U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A benefit claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed benefit claim under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

If the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference was submitted in an oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its

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inclusion on the first filing receipt, the petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required. Applicant is still required to submit the reference in compliance with 37 CFR 1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

### ***Information Disclosure Statement***

The information disclosure statement filed January 15, 2008 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. Non-patent literature has been listed in IDS but the applicant failed to provide a copy of each publication.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 49, 57-64 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 49, the amended claim presented in the preliminary amendment filed on April 03, 2008, is drawn to a compound 1-oxo-2-(2,6-dioxopiperidin-3-yl)-4-methylisoindoline for treating macular degeneration. The examiner reviewed the claims in context with original specification and the specification does not contain the written support for the claims as amended for this specific instant compound, 1-oxo-2-(2,6-dioxopiperidin-3-yl)-4-methylisoindoline. The examiner noted the description of the various derivatives of the instant compound claimed in claim 49 (Specification - page 7 line 25-26, page 9 line 27 formula, page 13 line 12 formula, page 14 line 14 formula, page 15 line 2 formula, page 17 line 27 formula). However the applicant does not demonstrate the preparation of the specific compound 1-oxo-2-(2,6-dioxopiperidin-3-yl)-4-methylisoindoline at the time of the invention for the treatment as claimed. The examiner is not clear, the compound, 1-oxo-2-(2,6-dioxopiperidin-3-yl)-4-methylisoindoline is prepared or obtained from other sources at the time of the invention and if it is prepared the specification is not providing any details. Claims 57 -64 are rejected which reads on the claim 49.

### **Claim Rejections – 35 USC § 103**

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 49, 61 and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over D' Amato, US Patent 6,469,045 (listed in Information Disclosure Statement).  
in view of Wolff, M.E. *Burger's Medicinal Chemistry 4<sup>th</sup> Ed. Part I*, Wiley: New York, **1979**, 336-337.

Claim 49 is drawn to a method of treating macular degeneration, which comprises administering to patient in need thereof a pharmaceutically effective amount of 1-oxo-2-(2,6-dioxopiperidin-3-yl)-methyloindoline (a thalidomide derivative) or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.

D' Amato teaches a compound without a methyl group with the exact same core structure as claimed in the instant claims (Figure 1, 2<sup>nd</sup> formula in the top from left) where all the variables are H, alkyl analogs of the instant claims, are *prima facie* obvious and require no secondary teaching. In addition D'Amato in general teaches the alkyl substitution, e.g. methyl to the compounds with general formulae (Column 7 formula A with various substitution including methyl group as in column 8 line 25 – 30). Moreover Wolff teaches that the addition of alkyl groups to active pharmacological agents often improves activity and bioavailability by increasing lipophilicity (See the examples in Table 8.2 of a local anesthetic SAR pg. 337 of Wolff).

It is clear that the prior art differs only in the presence of a methyl group. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use analogs of those of D' Amato to produce the instant invention. Analogous differing only in the substitution of hydrogen with methyl, are *prima facie* obvious, and require no secondary teaching. However D'Amato in general teaches the

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alkyl substitution, e.g. methyl to the compounds with general formulae. Moreover, the examiner provides the Wolff teaching to show this fact. One of the ordinary skill in the art would be motivated to prepare these compounds on the expectation that such close analogues would have similar properties and upon the routine nature of such experimentation in the art of medicinal chemistry. It would be routine for the chemist to insert a methyl group in order to increase potency and to establish better patent protection for the inventive compounds. The teachings of D' Amato makes it *prima facie* obvious to one of ordinary skill in the art at the time of the invention to develop a method of treating macular degeneration with analogues of the instant compound.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

One of ordinary skill is also one of "ordinary creativity, not an automaton". See *Leapfrog Enterprises Inc. v. Fisher-Price. and Mattel Inc.* UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT "An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. , 2007 U.S. LEXIS 4745, 2007 WL 1237837, at 12 (2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

Claim 61 is drawn to the method of claim 49 wherein the macular degeneration is wet macular degeneration, dry macular degeneration, age-related macular



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degeneration, age-related maculopathy, choroidal neovascularisation, retinal pigment epithelium detachment, atrophy of retinal pigment epithelium, Best's disease, vitelliform, Stargardt's disease, juvenile macular dystrophy, fundus flavimaculatus, Behr's disease, Sorsby's disease, Doyne's disease, honeycomb dystrophy, or macular damaging condition.

D' Amato teaches several categories of macular degeneration like Best's disease, Stargardt's diseases, neovascularization retinopathy, uveitis and vitritis (Column 2 line 23-39).

Claim 62 is drawn to the method of claim 49 wherein the compound is stereomerically pure.

D' Amato teaches the preparation of enrichment of optically active enantiomers, thus stereomerically pure compounds (Column 12 line 34-44).

Claims 57-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over D' Amato, US Patent 6,469,045 (listed in Information Disclosure Statement) as applied to claims 49, 61 and 62 above, and further in view of Bilodeau et al US Application Number US 2002/0137755.

Claim 57 is drawn to the method of claim 49 (claim 49 is unpatentable as stated above) wherein the method comprises administering a therapeutically effective amount of a second agent.

Claim 58 is drawn to the method of claim 57 wherein the second active agent is a steroid, a light sensitizer, an integrin, an antioxidant, an interferon, a xanthine derivative,

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a growth hormone, a neutrotrophic factor, a regulator of neovascularization, an anti-VEGF antibody, a prostaglandin, an antibiotic, a phytoestrogen, an anti-inflammatory compound or an antiangiogenesis compound.

Claim 59 is drawn to the method of claim 57 wherein the second active agent is thalidomide, verteporfin, purlytin, an angiostatic steroid, rhuFab, interferon-2.alpha. or pentoxifylline, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

Claim 60 is drawn to the method of claim 58 wherein the antiangiogenesis compound is thalidomide.

D' Amato teaches the treatment of ocular neovascular diseases associated with angiogenesis (Column 1 line 65-66) including macular degeneration (column 2 line 3-6) with antiangiogenesis compounds like thalidoamide derivatives. However it does not disclose the use of a second compound for the treatment. Bilodeau et al teaches the use of therapeutically effective amount of several second compounds like antiangiogenesis agents (Page 63 claims 35 and 36) for diseases related to angiogenesis including macular degeneration. Bildeau et al teaching include modulators of hormone receptor, retinoid receptor, cytotoxic and antiproliferative agents and enzyme inhibitor which could encompass compounds claimed as a second agent in claim 58 (Page 63 claim 22, 29 and 30). It also teaches the thalidomide as second agent as claimed in claim 59 and 60 (Page 15 [0259], page 63 claim 30).

It would have been obvious to one of the ordinary skill in the art at the time of invention to modify the method of D' Amato such that to have effective treatment of macular degeneration. Macular degeneration is the most common cause of visual

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damage and different treatment strategies are being developed. But a single treatment therapy is found to be less effective in treating macular degeneration. One of the ordinary skill in the art would have been motivated to achieve effective treatment for macular degeneration with therapeutically effective amount of derivatives of methylisoindoline with a second compound an anti antiangiogenesis. Since Bildeau et al teachings demonstrated that several diseases including macular degeneration can be treated with the combination of compounds, with a second compound in a composition one of ordinary skill in the art would have a reasonable expectation that such a modification would be successful. The combined teachings of D' Amato, in view of Bilodeau makes it prima facie obvious to one of ordinary skill in the art at the time of the invention to develop a method of treating macular degeneration with anti- angiogenesis derivatives as taught by D' Amato and including a second compound as taught by Bilodeau et al. "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850,205 USPQ 1069, 1072 (CCPA 1980)

Claims 63 and 64 are rejected under 35 U.S.C. 103(a) as being unpatentable over D' Amato, US Patent 6,469,045 (listed in Information Disclosure Statement) as applied to claims 49, 61 and 62 above in view of Kovesdi et al US Application Number US 2002/0137755.

D' Amato teaches the treatment of ocular neovascular diseases associated with angiogenesis (Column 1 line 65-66) including macular degeneration (column 2 line 3-6) with the analogues of instant compound in claim 49. However it does not teach the surgical intervention directed at reducing the symptoms of macular degeneration.

Kovesdi et al teaches the several intervention methods including surgical intervention as part of the treatment.

Claim 63 is drawn to the method of claim 49 wherein the compound is administered before, during or after surgical intervention directed at reducing or avoiding a symptom of macular degeneration in a patient.

Claim 64 is drawn to the method of claim 63 wherein the surgical intervention is light therapy, laser therapy, retinal pigment epithelium transplantation or foveal translocation.

Kovesdi et al teaches the several intervention methods as a part of a treatment regimen for macular degeneration. In addition the macular degeneration is treated along with other ocular therapies such as photodynamic therapy (light therapy), photocoagulation laser therapy, macular translocation or surgery (Page 10, paragraph [0066])

It would have been obvious to one of the ordinary skill in the art at the time of invention to modify the method of D' Amato such that to have effective treatment of macular degeneration. Macular degeneration is the common cause of visual damage in elderly people and different treatment strategies are being developed. It is known in the art that combining the surgical invention with pharmaceutical treatment is the effective

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way to avoid or reduce the symptoms in the population. One of the ordinary skill in the art would have been motivated to achieve effective treatment for macular degeneration with therapeutically effective amount of analogues of methylisoindoline with surgical intervention to reduce the symptoms. Since Kovesdi et al taught ocular related disorders can be treated with a treatment regimen involving intervention such as light and laser therapy one of ordinary skill in the art would have a reasonable expectation that such a modification would be successful. Kovesdi et al do not disclose the administration of the compound either before or during or after the surgical intervention however this is an empirical method in the art and vary according the treatment and hence this would be obvious to one of ordinary skill in the art. The combined teachings of D' Amato, in view of Kovesdi et al makes it prima facie obvious to one of ordinary skill in the art at the time of the invention to develop a method of reducing the symptoms of macular degeneration with the analogues of the compounds as taught by D' Amato and with intervention therapy as taught by Kovesdi et al.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MANU MANOHAR whose telephone number is (571)270-5752. The examiner can normally be reached on Mon - Thu 9.00AM to 4.00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, PATRICK Nolan can be reached on 571-272-0847. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent

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